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Letter to the Editor

## Positive clinical outcomes following ivacaftor treatment in a cystic fibrosis patient with the genotype 3272–26A > *G*/Q493X

Dear Editors,

In 2017 the EXPAND clinical trial [1] reported ivacaftor efficacy in cystic fibrosis patients heterozygous for residual function CFTR mutations and the F508del mutation. Although it is anticipated that the reported outcomes would translate into clinical efficacy in residual function patients without F508del on the second allele, there is no clinical data to support such an assumption. We present a case of sustained improvements in several different clinical domains following ivacaftor treatment in a cystic fibrosis patient with the functional class 5 CFTR mutation 3272–26A > *G* and a functional class 1 mutation in compound heterozygosity.

A 35-year-old lady diagnosed with cystic fibrosis during newborn screening had been a long-standing patient of our cystic fibrosis service. Genotyping had previously confirmed 2 cystic fibrosis-causing mutations; Q493X a functional class 1 mutation and 3272–26A > *G*, a class 5 mutation. Sweat chloride was elevated at 104 mmol/L. Although lung function was reasonably well preserved, she had significant upper lobe bronchiectasis on CT imaging of the thorax. Sputum had repeatedly cultured methicillin sensitive *staphylococcus aureus*, however *pseudomonas aeruginosa* eradication therapy had been required on 2 separate occasions previously. Routine treatment for her bronchiectasis included daily nebulised dornase alfa, twice-daily nebulised 6% saline and salmeterol-fluticasone metered dose inhaler. She had previously taken azithromycin 500 mg 3 times a week, however this had been discontinued several years earlier following a single isolation of *Mycobacterium abscessus*. She was adherent to daily airway clearance and twice weekly aerobic exercise to assist with sputum clearance. She had an extensive history of sinus disease that had previously required surgery and maintenance therapy with daily sinus douching and topical corticosteroids. In keeping with the presence of a functional class 5 mutation on one allele, the patient was pancreatic sufficient and had previously experienced episodes of acute pancreatitis.

Ivacaftor treatment was commenced initially on a trial basis and was self-funded. Several pertinent measurements were made at baseline and during the 2-month trial period. In the month leading up to commencing treatment and during the initial trial period, baseline therapies remained unchanged to avoid influencing any measured outcomes that may otherwise inform the decision to continue therapy. The patient noticed improvements in both upper and lower respiratory tract health, which were reflected in clinically meaningful changes in the Sino-Nasal Outcome Test (SNOT-22) and the Revised Cystic Fibrosis Quality of Life Questionnaire (CFQ-R) respiratory domain (Table 1). Quality of life improvements were also evident from improvements in the physical, vitality and health domains of the CFQ-R. Lung function improved markedly during the 2-month trial period and was sustained at 1-year post initiation of treatment. Cardiopulmonary exercise test was performed at baseline and at 2 months, which demonstrated improvements in workload and $VO_2$ peak. The patient had not made any changes to her routine exercise programme. Notable improvements were also seen on CT scan of chest, which demonstrated interval improvement in the extent of the mucus plugging after 2 months of treatment. The patient also had a 3.4 kg increase in weight during the first 2 months without any changes to diet. Despite the documented clinical improvements, there was no change observed in the sweat chloride before and after treatment.

**Table 1**
Clinical measurements at baseline and during first year of ivacaftor treatment.

| | Baseline | 4 weeks | 8 weeks | 1 year |
|---|---|---|---|---|
| SNOT-22 | 66 | 47 | 28 | 18 |
| CFQ-R (Respiratory) | 66.7 | 72.2 | 83.3 | 88.9 |
| CFQ-R (Physical) | 66.7 | 83.3 | 91.7 | 100 |
| CFQ-R (Vitality) | 33.3 | 41.7 | 50 | 75 |
| CFQ-R (Health) | 33.3 | 44.4 | 77.8 | 88.9 |
| $FEV_1$ (Litres) | 3.82 | 4.32 | 4.21 | 4.20 |
| $FEV_1$ (% predicted) | 102 | 116 | 114 | 113 |
| CPET Workload (Watts) | 165 | – | 210 | – |
| $VO^2$ peak (L/min/kg) | 24.9 | – | 29.4 | – |
| Weight (kg) | 75.0 | 75.9 | 78.4 | 78.4 |
| BMI ($kg/m^2$) | 23.7 | 24.0 | 24.7 | 24.7 |
| Sweat chloride (mmol/L) | 104 | 104 | 101 | – |

Legend: SNOT-22 = Sino-nasal outcome test (higher score reflecting poorer quality of life; minimal clinically important difference 12 points); CFQ-*R* = Revised Cystic Fibrosis Quality of Life Questionnaire (higher score reflecting better quality of life; minimal clinically important difference 4.0 points). CPET = Cardiopulmonary exercise test.

In the EXPAND clinical trial, compound heterozygotes carrying 3272–26A > *G* and F508del mutations treated with ivacaftor alone or in combination with the CFTR corrector tezacaftor demonstrated significant improvements in $FEV_1$ (3.5% and 5.7% respectively) [1]. The greater benefits observed with combination therapy likely reflect modulation of both F508del and 3272–26A > *G* CFTR alleles. The improvements observed with single agent ivacaftor however are most likely predominantly a consequence of ivacaftor potentiation of 3272–26A > *G* alone as ivacaftor treatment in F508del homozygotes has demonstrated only a minimal clinical effect, which was not significantly different from placebo [2]. It is therefore reasonable to expect that ivacaftor may provide beneficial results in a compound heterozygote patient with 3272–26A > *G* on one allele and a mutation not predicted to respond to potentiation on the other, as in this case. There is however, to our knowledge, no published data on the use of ivacaftor in patients with a 3272–26A > *G* mutation in the absence of F508del. It is interesting that there was no change observed in the sweat chloride in the reported case.

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However the discrepancy between clinical improvement and sweat chloride change following treatment with ivacaftor has previously been described [3].

While important to acknowledge the lack of generalizability of this single patient case study, it is nevertheless conceivable that similar clinical benefits may also be observed in patients with other residual function mutations (known to respond to ivacaftor potentiation when in trans with F508del) despite not having an F508del mutation on their second allele. In vitro studies using human bronchial epithelial lines expressing missense CFTR variants with residual function have demonstrated improved CFTR function with the CFTR corrector lumacaftor and more so with a combination of lumacaftor and ivacaftor [4]. This suggests that patients with residual function genotypes (without F508del on the second allele) may actually experience greater clinical benefit from dual therapy that incorporates a corrector such as lumacaftor or tezacaftor. Furthermore, the triple modulator therapy Elexacaftor-Tezacaftor-Ivacaftor, which has demonstrated impressive efficacy in patients with an F508del/minimal function genotype [5] is now also being studied in patients with residual function mutations [6]. Similarly to the trials with tezacaftor-ivacaftor however, this study design again requires the participant to have an F508del mutation on the second allele.

In summary, we present a case of sustained significant improvements in several different clinical domains following initiation of ivacaftor treatment in a CF patient with a 3272–26A > *G* mutation and a functional class 1 mutation in compound heterozygosity. It is hoped that this relatively small population of patients will not be overlooked when funding decisions are made by health services regarding CFTR modulator eligibility.

## Declaration of Competing Interest

M Pallin and CP Daley do not have any conflicts of interest to disclose.

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